

### REMARKS

The Office Action of July 26, 2007, has been received and reviewed. Claims 1-63 are currently pending in the application. Claims 11 and 18-20 were previously withdrawn from consideration. Claims 1-10, 12-17, and 21-63 are under consideration. Claims 1-10, 12-17, and 21-63 stand rejected. Claims 5, 12, and 62 are objected to. Claims 1, 2, 5, 12, 13, 21, 22, 24, 31-34, 37, 43, 44, 46, 48, 55, 56, 62, and 63 are amended herein. New claim 64 is presented herein. Basis for new claim 64 can be found throughout the Specification and more specifically in ¶¶ 14, 31, 32, 42, 43, 52, and 53. All amendments are made without prejudice or disclaimer. No new matter has been presented. Reconsideration is respectfully requested.

#### Claim Objections

##### Claim 5

Claim 5 stands objected to as it appears to the Examiner that “further” is missing between “is” and “transformed.” Applicant respectfully submits that appropriate correction has been made.

##### Claim 12

Claim 12 stands objected to as “a” is not required before *Lactococcus* species. Applicant respectfully submits that appropriate correction has been made.

##### Claim 62

Claim 62 stands objected to as a period is missing at the end of the claim. Applicant respectfully submits that appropriate correction has been made.

##### Claims 22 and 62

The Examiner asserts that if claim 22 is found allowable, claim 62 will be objected to as being a substantial duplicate thereof. Applicant respectfully submit that, given the amendments to claims 21, 22, and 62, claims 22 and 62 can no longer be considered substantial duplicates.

Further, applicant note that claim 22 depends from claim 21, which recites that means for encoding an inactive *Lactococcus* thymidylate synthase be incorporated into the genome. Applicant notes that there is no corresponding recitation in claim 62. Thus, claims 22 and 62 should not be considered substantial duplicates.

**Rejections Under 35 U.S.C. § 102(b)**

Claims 1-10, 12-17, 21, 23-30, 32, and 34-61 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Ross *et al.* (App. Environ. Micro. (1990), Vol. 56, pp. 2156-2163) (hereinafter “Ross”). Specifically, it was asserted that the *thyA* gene disclosed therein is construed as a mutant of SEQ ID NOs: 3 and 5. Office Action mailed July 26, 2007, at page 9. Applicant respectfully traverses the rejections as hereinafter set forth.

Applicant note that “a claim is only anticipated if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). Applicant respectfully asserts that claims 1-10, 12-17, 21, 23-30, 32, and 34-61 cannot be anticipated by Ross as Ross does not teach each and every element of these claims.

Specifically, Ross does not teach “a nucleic acid [or means for] encoding an inactive *Lactococcus* thymidylate synthase” or “a defect in said *Lactococcus* thymidylate synthase gene which inactivates the *Lactococcus* thymidylate synthase encoded therein” as recited in amended claims 1, 21, 32, and 43. Basis for the amendments to claims 1, 21, 32, and 43 can be found throughout the Specification and more specifically in ¶¶ 14, 31, 32, and 35 of the application as published. Consequently, Ross cannot anticipate claims 1, 21, 32, and 43. As such, applicant respectfully requests the withdrawal of the rejections of claims 1, 21, 32, and 43 under 35 U.S.C. § 102(b) and reconsideration of same.

In addition, applicant respectfully submits that Ross cannot anticipate claims 2-10, 12-17, 23-30, 34-42 and 44-61, *inter alia*, as each of these claims depends, directly or indirectly, from one of non-anticipated claims 1, 21, 32, and 43. Consequently, applicant respectfully requests the withdrawal of the rejections of claims 2-10, 12-17, 23-30, 34-42 and 44-61 under 35 U.S.C. § 102(b) and reconsideration of same.

**Rejections Under 35 U.S.C. § 112, Second Paragraph**

**“Defective” or “Defect”**

Claims 1-10, 12-17, and 21-63 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite. Specifically, it was asserted that “defective” or “a defect” was indefinite as it was thought impossible to know what kind of defect was introduced (*i.e.*, does the defect result in an active or inactive thymidylate synthase). Office Action mailed July 26, 2007, at page 7. Applicant respectfully traverses the rejections as hereinafter set forth.

Although the applicant does not agree that any of the claims are indefinite, to expedite prosecution, claims 1, 2, 21, 22, 32, 33, 34, 43, 44, 62, and 63 have been amended herein. Specifically, claims 1, 2, 21, 22, 32, 33, 34, 62, and 63 have been amended to no longer recite “defective” or “a defect.” Further, claims 43 and 44 have been amended so as to specify the type of defect; to wit: “an inactivating defect.” Thus, applicant respectfully submits that claims 1, 2, 21, 22, 32, 33, 34, 43, 44, 62, and 63 can no longer be considered indefinite for failing to define the type of defect. Consequently, applicant respectfully requests the withdrawal of the rejections of claims 1, 2, 21, 22, 32, 33, 34, 43, 44, 62, and 63 under 35 U.S.C. § 112, second paragraph, and reconsideration of same.

In addition, claims 3-10, 12-17, 23-31, 35-42, and 45-61 are not indefinite, *inter alia*, as each of these claims depends, directly or indirectly, from one of definite claims 1, 2, 21, 22, 32, 33, 34, 43, and 44. As such, applicant respectfully requests the withdrawal of the rejections of claims 3-10, 12-17, 23-31, 35-42, and 45-61 under 35 U.S.C. § 112, second paragraph, and reconsideration of same.

**Claim 5**

Claim 5 stands rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite. Specifically, it was asserted that the metes and bounds of the term “functional thymidylate synthase gene” were unclear as a gene may have different function in addition to encoding the synthase at issue. Office Action mailed July 26, 2007, at page 8. Applicant respectfully traverses the rejection as hereinafter set forth.

Although the applicant does not agree that any of the claims are indefinite, to expedite prosecution, claim 5 has been amended herein. Specifically, claim 5 has been amended to recite “wherein said transforming plasmid does not encode an active thymidylate synthase” in place of “wherein said transforming plasmid does not comprise a functional thymidylate synthase gene.” Thus, it is no longer unclear as to what function of the gene is being affected as the function of encoding a specific enzyme is recited. In view of at least the foregoing, applicant respectfully requests the withdrawal of the rejection of claim 5 under 35 U.S.C. § 112, second paragraph, and reconsideration of same.

#### Claim 21

Claim 21 stands rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite. Specifically, it was asserted that every bacterium comprises a genome and that the metes and bounds of the term “means” were unclear. Office Action mailed July 26, 2007, at page 8. Applicant respectfully traverses the rejection as hereinafter set forth.

Although the applicant does not agree that any of the claims are indefinite, to expedite prosecution, claim 21 has been amended herein. Specifically, claim 21 has been amended to no provide “a genome,” but to refer instead to the genome which the Examiner agrees every bacterium comprises. Thus, claim 21 may no longer be considered unclear for the recitation of “a genome.”

Regarding the term “means,” applicant note that “means for,” as recited in claim 21, has a specific definition attributed to it by paragraph six of 35 U.S.C. § 112; to wit: “[a]n element in a claim for a combination may be expressed as a means or a step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claims shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.” Thus, the recitation of “means for” is not indefinite, it has the precise definition provided by paragraph six of 35 U.S.C. § 112 (*see* M.P.E.P. §§ 2181-2186).

In view of at least the foregoing, applicant respectfully requests the withdrawal of the rejection of claim 21 under 35 U.S.C. § 112, second paragraph, and reconsideration of same.

Claims 22, 31, and 33

Claims 22, 31, and 33 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite. Specifically, it was asserted that the claims were “confusing as reciting ‘a strain of *Lactococcus* bacterium comprises a thymidylate synthase gene selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5.’” Office Action mailed July 26, 2007, at page 7. Applicant respectfully traverse the rejections as hereinafter set forth.

Although the applicant does not agree that any of the claims are indefinite, to expedite prosecution, claims 22, 31, and 33 have been amended herein. Specifically, claims 22 and 31 have been amended to recite: “said strain of *Lactococcus* bacterium comprises a nucleotide sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5;” and claim 33 has been amended to recite: “said thymidylate synthase gene comprises a nucleotide sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5.” Thus, applicant respectfully asserts that claims 22, 31, and 33 can no longer be considered indefinite for the recitation of “a strain of *Lactococcus* bacterium comprises a thymidylate synthase gene selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5.” In view of at least the foregoing, applicant respectfully requests the withdrawal of the rejection of claims 22, 31, and 33 under 35 U.S.C. § 112, second paragraph, and reconsideration of same.

Rejections under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 21, 23-30, 43-61, and 63 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly failing to comply with the written description requirement. Specifically, it is asserted that the Specification fails to define those structural features of *Lactococcus* thymidylate synthase gene(s) that are commonly possessed by members of the genus that distinguish them from others.” Office Action mailed July 26, 2007, at page 5. Applicant respectfully traverses the rejections as hereinafter set forth.

As a preliminary matter, applicant note that the claims, as amended, are no longer generally directed to defective thymidylate synthase genes, but to nucleic acids encoding an inactive thymidylate synthase.

In the case of *Falkner v. Inglis* (448 F.3d 1357 (Fed. Cir. 2006)), the Federal Circuit noted that “there is no *per se* rule that an adequate written description of an invention that involved a biological macromolecule must contain a recitation of known structure.” *Falkner* at 1366. Further, the court noted that “when the prior art includes the . . . information, precedent does not set a *per se* rule that the information must be determined afresh.” *Id.* at 1367. Accordingly, the Court held that “where . . . accessible literature sources clearly provide[], as of the relevant date, . . . sequences, satisfaction of the written description requirement does not required either the recitation or incorporation by reference of such . . . sequences. *Id.* at 1368.

Applicant respectfully submits that such a situation is at issue in the present application. Thymidylate synthases from *Lactococcus* are well known and their structures are highly conserved. As evidence of such, applicant provide a sequence alignment among the eight known thymidylate synthases from *Lactococcus* (as available in PubMed) along with SEQ ID NOs: 4 and 6 (which are the enzymes encoded by SEQ ID NOs: 3 and 5, respectively):

18539502	1	MTYADQVFKQNIQNILDNGVFSENARPKYKDGQMANSKYV
SEQID6	1	MTYADQVFKQNIQNILDNGVFSENARPKYKDGQMANSKYV
124492611	1	MTYADQVFKQNIQNILDNGVFSENARPKYKDGQMANSKYV
125623803	1	MTYADQVFKQNIQNILDNGVFSENARPKYKDGQMANSKYV
116512335	1	MTYADQVFKQNIQNILDNGVFSENARPKYKDGQMANSKYV
SEQID4	1	MTYADQVFKQNIQNILDNGVFSENARPKYKDGQMANSKYV
13638515	1	MTYADKIFKQNIQNILDNGVFSENARPKYKDGQTANSKYV
15673523	1	MTYADKIFKQNIQNILDNGVFSENARPKYKDGQTANSKYV
12724542	1	MTYADKIFKQNIQNILDNGVFSENARPKYKDGQTANSKYV
13310416	1	MTYADKIFKQNIQNILDNGVFSENARPKYKDGQTANSKYV

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18539502	41	TGSFVTTYDLQKGEFPITTLRPIPIKSAIKELMWIYQDQTS
SEQID6	41	TGSFVTTYDLQKGEFPITTLRPIPIKSAIKELMWIYQDQTS
124492611	41	TGSFVTTYDLQKGEFPITTLRPIPIKSAIKELMWIYQDQTS
125623803	41	TGSFVTTYDLQKGEFPITTLRPIPIKSAIKELMWIYQDQTS
116512335	41	TGSFVTTYDLQKGEFPITTLRPIPIKSAIKELMWIYQDQTS
SEQID4	41	TGSFVTTYDLQKGEFPITTLRPIPIKSAIKELMWIYQDQTS
13638515	41	TGSFVTTYDLQKGEFPITTLRPIPIKSAIKELMWIYQDQTS
15673523	41	TGSFVTTYDLQKGEFPITTLRPIPIKSAIKELMWIYQDQTS
12724542	41	TGSFVTTYDLQKGEFPITTLRPIPIKSAIKELMWIYQDQTS
13310416	41	TGSFVTTYDLQKGEFPITTLRPIPIKSAIKELMWIYQDQTS

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18539502	81	ELSVLEEKYGVKYWGEWGIGDGTIGQRYGATVKKYNIIGK
SEQID6	81	ELSVLEEKYGVKYWGEWGIGDGTIGQRYGATVKKYNIIGK
124492611	81	ELSVLEEKYGVKYWGEWGIGDGTIGQRYGATVKKYNIIGK
125623803	81	ELSVLEEKYGVKYWGEWGIGDGTIGQRYGATVKKYNIIGK
116512335	81	ELSVLEEKYGVKYWGEWRIGDGTIGQRYGATVKKYNIIGK
SEQID4	81	ELSVLEEKYGVKYWGEWGIGDGTIGQRYGATVKKYNIIGK
13638515	81	ELAILLEEKYGVKYWGEWGIGDGTIGQRYGATVKKYNIIGK
15673523	81	ELAILLEEKYGVKYWGEWGIGDGTIGQRYGATVKKYNIIGK

12724542	81	ELAILLEEKYGVKYWGEWGIGDGTIGQRYGATVKKYNIIGK
13310416	81	ELAILLEEKYGVKYWGEWGIGDGTIGQRYGATVKKYNIIGK

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18539502	121	LLEGLAKNPWNRRNIINLWQYEDFEETEGLLPCAFQTMFD
SEQID6	121	LLEGLAKNPWNRRNIINLWQYEDFEETEGLLPCAFQTMFD
124492611	121	LLEGLAKNPWNRRNIINLWQYEDFEETEGLLPCAFQTMFD
125623803	121	LLEGLAKNPWNRRNIINLWQYEDFEETEGLLPCAFQTMFD
116512335	121	LLEGLAKNPWNRRNIINLWQYEDFEETEGLLPCAFQTMFD
SEQID4	121	LLEGLAKNPWNRRNIINLWQYEDFEETEGLLPCAFQTMFD
13638515	121	LLDGLAKNPWNRRNIINLWQYEDFEETEGLLPCAFQTMFD
15673523	121	LLDGLAKNPWNRRNIINLWQYEDFEETEGLLPCAFQTMFD
12724542	121	LLDGLAKNPWNRRNIINLWQYEDFEETEGLLPCAFQTMFD
13310416	121	LLDGLAKNPWNRRNIINLWQYEDFEETEGLLPCAFQTMFD

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18539502	161	VRREKDGQIYLDATLIQRSNDMLVAHHINAMQYVALQMMI
SEQID6	161	VRREKDGQIYLDATLIQRSNDMLVAHHINAMQYVALQMMI
124492611	161	VRREKDGQIYLDATLIQRSNDMLVAHHINAMQYVALQMMI
125623803	161	VRREKDGQIYLDATLIQRSNDMLVAHHINAMQYVALQMMI
116512335	161	VRREKDGQIYLDATLIQRSNDMLVAHHINAMQYVALQMMI
SEQID4	161	VRREKDGQIYLDATLIQRSNDMLVAHHINAMQYVALQMMI
13638515	161	VRREQDGQIYLDATLIQRSNDMLVAHHINAMQYVALQMMI
15673523	161	VRREQDGQIYLDATLIQRSNDMLVAHHINAMQYVALQMMI
12724542	161	VRREQDGQIYLDATLIQRSNDMLVAHHINAMQYVALQMMI
13310416	161	VRREQDGQIYLDATLIQRSNDMLVAHHINAMQYVALQMMI

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18539502	201	AKHFSWKVGKFFFYFVNNLHIYDNQFEQANELMKRTASEKE
SEQID6	201	AKHFSWKVGKFFFYFVNNLHIYDNQFEQANELMKRTASEKE
124492611	201	AKHFSWKVGKFFFYFVNNLHIYDNQFEQANELMKRTASEKE
125623803	201	AKHFSWKVGKFFFYFVNNLHIYDNQFEQANELMKRTASEKE
116512335	201	AKHFSWKVGKFFFYFVNNLHIYDNQFEQANELMKRTASEKE
SEQID4	201	AKHFSWKVGKFFFYFVNNLHIYDNQFEQANELMKRTASEKE
13638515	201	AKHFSWKVGKFFFYFVNNLHIYDNQFEQANELVKRTASDKE
15673523	201	AKHFSWKVGKFFFYFVNNLHIYDNQFEQANELVKRTASDKE
12724542	201	AKHFSWKVGKFFFYFVNNLHIYDNQFEQANELVKRTASDKE
13310416	201	AKHFSWKVGKFFFYFVNNLHIYDNQFEQANELVKRTASDKE

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18539502	241	PRLVLNVPDGTNFFDIKPEDFELVDYEPVKPQLKFDLAI
SEQID6	241	PRLVLNVPDGTNFFDIKPEDFELVDYEPVKPQLKFDLAI
124492611	241	PRLVLNVPDGTNFFDIKPEDFELVDYEPVKPQLKFDLAI
125623803	241	PRLVLNVPDGTNFFDIKPEDFELVDYEPVKPQLKFDLAI
116512335	241	PRLVLNVPDGTNFFDIKPEDFELVDYEPVKPQLKFDLAI
SEQID4	241	PRLVLNVPDGTNFFDIKPEDFELVDYEPVKPQLKFDLAI
13638515	241	PRLVLNVPDGTNFFDIKPEDFELVDYEPVKPQLKFDLAI
15673523	241	PRLVLNVPDGTNFFDIKPEDFELVDYEPVKPQLKFDLAI
12724542	241	PRLVLNVPDGTNFFDIKPEDFELVDYEPVKPQLKFDLAI
13310416	241	PRLVLNVPDGTNFFDIKPEDFELVDYEPVKPQLKFDLAI

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As can be seen from the alignments, all of the known *Lactococcus* thymidylate synthase enzymes are extremely highly conserved. The Specification, in combination with the known *Lactococcus* thymidylate synthase enzymes, provides a more than adequate description of the structural features of *Lactococcus* thymidylate synthases that are commonly possessed by members of the

genus that distinguish them from others non-*Lactococcus* thymidylate synthase enzymes. Thus, and in view of the holding of the Court in *Falkner*, applicant respectfully submits that claims 21, 23-30, 43-61, and 63 are adequately described within the meaning of 35 U.S.C. § 112, first paragraph. Consequently, applicant respectfully requests the withdrawal of the rejections of claims 21, 23-30, 43-61, and 63 under 35 U.S.C. § 112, first paragraph, for lack of written description, and reconsideration of same.

**Rejections under 35 U.S.C. § 112, First Paragraph, Enablement**

Claims 21, 23-30, 43-61, and 63 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly failing to comply with the enablement requirement. Specifically, it is asserted that the Specification “does not reasonably provide enablement for a *Lactococcus* bacterium comprising a disrupted thymidylate synthase gene having 5’ and 3’ regions with less than 90% identity to SEQ ID NOs: 1 and 2 or an undefined percent identity to SEQ ID NOs: 3 or 5. It does not provide enablement for a defect in TS gene other than resulting in encoding an inactive thymidylate synthase.” Office Action mailed July 26, 2007, at page 6. Applicant respectfully traverses the rejections as hereinafter set forth.

As a preliminary matter, applicant notes that the claims, as amended, are no longer generally directed to defective thymidylate synthase genes, but to nucleic acids encoding an inactive thymidylate synthase. Thus, the claims should now be enabled as Examiner notes that the Specification “does not provide enablement for a defect in TS gene other than resulting in encoding an inactive thymidylate synthase.” Applicant notes that it is a bacterium comprising these nucleotide sequences encoding an inactive thymidylate synthase which is now claimed.

In regards to the Examiner remarks concerning “an undefined percent identity to SEQ ID NOs: 3 or 5,” applicant note, as shown in the alignment above, that thymidylate synthases from *Lactococcus* are extremely highly conserved. Thus, one of ordinary skill in the art would conclude that the percent identity to enzymes encoded by SEQ ID NOs: 3 and 5 may be undefined, it will be very high given the very high identity among the proteins at issue.



Further, the Examiner apparently asserts that a skilled person can only modify those members of the *Lactococcus* genus whose entire *thyA* locus (*i.e.*, the *thyA* coding region and the substantially long flanking sequences) are homologous to SEQ ID NOs: 3 or 5.

In contrast, as noted in ¶ 35 of the Specification, the present inventors isolated the *thyA* locus and flanking sequences from *Lactococcus lactis* MG1363 by probing with the *thyA* coding sequence as isolated by Ross *et al.* from an entirely different *Lactococcus* member (note that Ross *et al.* only include very short flanking sequence of 86 and 31 bp).

This is because – and substantiated in our previous submissions – the sequence identity between *thyA* coding regions of different *Lactococcus* members is very high, over 89%. Thus, applicants respectfully note that the Examiner's reliance on Ross, p.2160, col. 1, is misplaced as therein *thyA* is aligned with *thyA* genes from non-cocci or even to *thyA* from eukaryotes and viruses.

Consequently, all that a person skilled in the art needs to do is to isolate nucleic acid sequences comprising the *thyA* coding region using standard hybridization with probes directed to said, highly homologous, *thyA* coding region. Having so retrieved a clone encompassing the *thyA* coding region, it is well within the ordinary skill in the art to apply standard techniques such as cloning or inverse PCR (*see, e.g.*, Leong 1991 submitted herewith) to isolate the sequences flanking said *thyA* coding sequence, irrespective of whether said flanking sequences do or do not show homology to the *thyA* flanking sequences from other *Lactococcus* members.

Thus, armed with the teachings of the Specification, one ordinarily skilled in the art could readily obtain the flanking sequences of *thyA* genes from any *Lactococcus* member without undue experimentation and put this to use to arrive at any *thyA*-deficient member of the *Lactococcus* genus.

In view of at least the foregoing, applicant respectfully requests the withdrawal of the rejections of claims 21, 23-30, 43-61, and 63 under 35 U.S.C. § 112, first paragraph, for lack of enablement and reconsideration of same.

**CONCLUSION**

In light of the above amendments and remarks, applicant respectfully requests reconsideration of the application. If questions remain after consideration of the foregoing, or if the Office should determine that there are additional issues which might be resolved by a telephone conference, the Office is kindly requested to contact applicant's attorney at the address or telephone number given herein.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Dan J. Morath', with a long horizontal flourish extending to the right.

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